--18 (amended). A fusion protein [comprising] presenting epitopes of at least two autoantigens selected from the group consisting of glutamic acid decarboxylase, islet cell antigen and preproinsulin, wherein said fusion protein comprises a label.--

REMARKS

Filing Date

This application was filed as a Continued Prosecution Application on 28 July 2000. It is believed that the application should have this filing date although it receives the benefit of an earlier date. This date of 28 July 2000 is shown above although the Office Action still shows a filing date of 29 January 1998.

The 35 U.S.C. § 103(a) Rejections

Claims 1-5, 7-10 and 17 were rejected under 35 U.S.C. § 103(a) as being obvious over Rogers et al. in view of Hummel et al., Verge et al., Rabin et al, Borg et al., Berg et al. and Wiest-Ladenburger et al.

Attached is a Declaration Under 37 C.F.R. § 131 by Applicant stating that he was in possession of the claimed invention at least as early as 22 August 1996. The exhibits attached to the Declaration indicate that Applicant had possession of the idea of using islet cell antibodies (ICAs) for an assay for diabetes at least as early as 22 August 1996. These exhibits had been submitted with the Response After Final which was filed 25 May 2000. Exhibit 1 was in the Finnish language and Exhibit 3 was a translation of Exhibit 1 into English. No Certificate of Verification had been filed with the 25 May 2000 Response. The Exhibits are here resubmitted (Exhibit 3 is now incorporated into Exhibit 1) together with a Certificate of Verification that the translation attached to Exhibit 1 was performed by a person proficient in both Finnish and English and that the translation is true and complete.

The ideas set forth in Exhibit 1 included the use of a fusion protein using epitopes from different ICA proteins (see page 6 of the translation of Exhibit 1). These notes further teach that such a fusion protein could include epitopes from GAD65 and ICA 512 (IA2). Insulin was also mentioned as an ICA (see page 1 of the translation of Exhibit 1). This date of 22 August 1996 predates both the Borg et al. and the Wiest-Ladenburger et al. references which have been relied

upon for the rejection. Both of those references are from 1997. Borg et al. was cited for its teaching that antibodies to GAD and IA2 are useful in the diagnosis of diabetes. The Declaration and Exhibits show that Applicant was in possession of this knowledge prior to the publication of the Borg et al. reference. The Wiest-Ladenburger et al. reference was cited for its teaching that in most individuals developing IDDM, ICAs are markers for the disease and that IA2 and GAD65 represent a major subfraction of ICAs. Again, the Declaration and Exhibits show that Applicant was in possession of this knowledge prior to the publication of the Wiest-Ladenburger et al. reference. In view of the Declaration and Exhibits showing conception of the invention prior to the publication dates of the two cited papers, it is urged that the Borg et al. and the Wiest-Ladenburger et al. references cannot be cited against the present invention.

The remaining references cited in the Office Action were in the prior art. The Office Action has urged that the claimed invention was obvious in view of the cited prior art which includes the Borg et al. and the Wiest-Ladenburger et al. references. Because these latter two references are predated by the invention, it is here urged that once the Applicant on his own, prior to the publication of the two references, discovered what is taught in the Borg et al. and the Wiest-Ladenburger et al. references, the claimed invention was necessarily obvious (as urged in the Office Action) to the Applicant who is one of skill in the art. But this recognition of the claimed invention required knowledge of what the Applicant had discovered on his own and what had not been previously published, specifically the information which was later published in the Borg et al. and the Wiest-Ladenburger et al. references. Because these two references were relied upon to make the rejection, it is urged that the rejection must fail and it is requested that the rejection be withdrawn.

The Office Action mailed 11 August 2000 states that even with a certified English translation of Exhibit 1 the Declaration together with the attached Exhibits would be insufficient to overcome the rejection. The reason set forth for such a conclusion is that the Declaration with Exhibits teaches a fusion protein comprising GAD65/ICA512/Glioma 38kd and does not teach a fusion protein including preproinsulin. It is urged that such reasoning is improper. The Declaration and Exhibits teach a fusion protein with flag epitope and flexible linker to combine the informative epitopes from different ICA proteins and gives *as an example* the GAD65/ICA512/38kD. The idea was not limited to this one fusion protein but was general for fusion proteins as described. The Borg et al. reference which is being predated by the

Declaration does not include any teaching of preproinsulin antibodies, rather it teaches only IA2 (ICA512) and GAD which were both clearly envisioned by the inventor at the time of creation of Exhibit 1. The Wiest-Ladenburger et al. reference similarly teaches only the IA2 and GAD65 antibodies and does not teach preproinsulin antibodies. It is urged that any teachings of the Borg et al. and the Wiest-Ladenburger et al. references were known by the inventor prior to the publication of the references as evidenced by the attached Declaration and Exhibits. The Exhibits do not specifically recite use of preproinsulin, but as urged in the Office Action, use of preproinsulin would have been obvious to one of skill in the art because of the prior art which taught autoantibodies to preproinsulin in patients with diabetes. Please note that, although use of preproinsulin was not specifically listed in the Exhibits, use of insulin (which is a processed and shortened form of preproinsulin) was listed (see page 1 of the English translation of Exhibit 1). It is therefore urged that the inventor was in possession of the claimed invention prior to the publication of the Borg et al. and the Wiest-Ladenburger et al. references. Because these references are predated by the Exhibits with the Declaration it is urged that they cannot be cited in a rejection of the pending claims. Because the rejection depends upon these references, it is urged that the rejection must fail and it is requested that the rejection be withdrawn.

Claims 1-10 and 17-18 were rejected under 35 U.S.C. 103(a) as obvious over Rogers et al., in view of Hummel et al., Verge et al., Rabin et al., Borg et al., Berg et al., and Wiest-Ladenburger et al. and further in view of WO 94/07464. The only difference between this rejection and that described above is the inclusion of WO 94/07464 as a teaching of biotin or streptavidin as part of the fusion protein which is a limitation of claim 6. As discussed just above, the rejection relies upon the Borg et al. and the Wiest-Ladenburger et al. references which, in view of the attached Declaration and Exhibits, cannot be cited against the claims of the present application. In view of this it is requested that the rejection be withdrawn.

Claims 19-20 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Rogers et al. in view of Hummel et al., Verge et al., Rabin et al., Borg et al., Berg et al., and Wiest-Ladenburger et al. and further in view of WO 94/07464 and Xu et al. or Hemmila et al. Again, the rejection relies upon the Borg et al. and the Wiest-Ladenburger et al. references. The attached

Declaration and references show conception of the invention prior to the publication of these two references. It is requested that this rejection be withdrawn.

In addition to overcoming two of the cited references which were relied upon, Applicant reiterates that the rejection should also fail for the reasons set forth in the Amendment filed on 16 December 1999. One point from the Remarks of the Amendment of 16 December 1999 will be further commented on. It was urged that the claimed fusion proteins would form a three dimensional structure with exposed epitopes not predictable from the cited prior art and therefore it would have been unpredictable whether any appropriate epitopes would be accessible to the antibodies to be used. The Office Action of 28 February 2000 responded to this argument by stating that there was no evidence of record to indicate the state of the art at the time the invention was made teaches that making fusion proteins comprising more than one epitope is unpredictable. That statement does not respond to the argument set forth in the Amendment. It was not urged that fusion proteins containing more than one epitope could not be made, rather it was urged that when several peptide fragments are linearly linked to form a large protein it was unpredictable at the time of the invention as to how such a synthetic protein would fold and whether it would fold in a manner which resulted in the known epitopes being exposed and available to react with antibodies. The three dimensional structures of such synthesized proteins was not known and was not predictable and it was not known what epitopes would be exposed. Submitted herewith are searches made of MedLine and of the Protein Data Bank. These searches were performed on May 17, 2000. None of the searches resulted in a finding of a reference which teaches the folding of GAD65 or ICA 512 (IA2). Because the folding of these proteins is not presently known, it is urged that the folding of these proteins at the time of the invention was also unknown and that the folding of a fusion protein comprising these proteins was unknown and unpredictable at the time of the invention. Because of the differences between the claims and the cited prior art, i.e., the fact that such recombitopes had never been made, that the claimed recombitopes can be very large, and that specific protein fragments were not clearly known to include appropriate epitopes, the prior art at best leads to an obvious to try analysis.

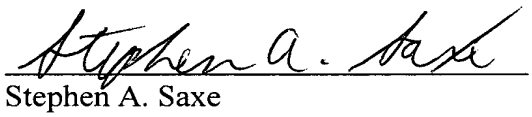
The Office Action mailed 11 August 2000 responded to the above arguments by stating that fusion proteins comprising fragments of more than one antigen or protein were well known in the art as evidenced by the Rogers et al. reference. It further states that the claims include no

limitation that the fusion protein must retain the three dimensional structure of the intact protein. Concerning the Rogers et al. reference, it is agreed that fusion proteins were known at the time of the invention. That is not the issue being argued by Applicant. What was not known and could not have been obvious was whether the fusion protein being claimed would fold in such a manner that it would present the required epitopes to be useful. As for the argument that the claims do not limit the fusion protein to the three dimensional structure of the intact protein, the claims have been amended to explicitly require that the fusion protein not merely have epitopes of the autoantigens but that they present these epitopes. This is not a new limitation because such a limitation was implicit in the claims in order for the claimed proteins to have utility and it is noted that no utility rejection was made. The change is being made at this time simply to make this implicit point explicit in view of the argument set forth in the Office Action.

In view of the arguments set forth above and in the Amendment submitted 16 December 1999, it is requested that the rejections of the claims under 35 U.S.C. § 103(a) be withdrawn.

In view of the amendments and the above arguments, it is submitted that the present claims satisfy the provisions of the patent statutes and are patentable over the prior art. Reconsideration of this application and early notice of allowance are requested.

Respectfully submitted,



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